Attorney's Docket No.: 09531-096001 / 99140

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Zoltan Kiss
Serial No. : 09/873,654
Filed : June 4, 2001
Title : COMPOSITIONS AND METHODS FOR STIMULATING WOUND HEALING AND FIBROBLAST PROLIFERATION

Art Unit : 1654
Examiner : Michael Meller

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Enclosed for submission in the above-identified application are the following:

1. Brief on Appeal (10 pages).
2. Check in the amount of $250.00.
3. Petition for Four-Month Extension of Time (1 page).
4. Check in the amount of $795.00.
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Respectfully submitted,

Date: June 17, 2005

M. Angela Parsons, Ph.D.
Reg. No. 44,282

Fish & Richardson P.C., P.A.
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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Mail Stop Appeal Brief - Patents
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BRIEF ON APPEAL

(1) Real Party in Interest

The real party of interest is the Regents of the University of Minnesota.

(2) Related Appeals and Interferences

None.

(3) Status of Claims

Claims 1, 4, 7-9, and 31 are pending and stand rejected. Claims 3, 5, 6, 10, 29, and 30 are withdrawn as directed toward non-elected species. Applicant notes that the Examiner indicated in the Office Action mailed May 18, 2004 that claim 27 was pending. Claim 27 was canceled in the Response to Office Action filed November 21, 2003, and is therefore not pending.

(4) Status of Amendments

All amendments have been entered

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(5) Summary of Claimed Subject Matter

In general, claims 1, 4, 7-9, and 31 are directed toward a composition for healing a skin wound in a patient. The composition includes placental alkaline phosphatase in an amount effective for stimulating proliferation of fibroblasts. The composition also includes a gel-forming material, and is formulated for topical delivery.

(6) Grounds of Rejection

(A) Claim 1 stands rejected under 35 U.S.C. §102(b) as being anticipated by SU 1138410.

(B) Claims 1, 7-9, and 27 stand rejected under 35 U.S.C. §103(a) as being unpatentable over SU 1814764 in view of Sugitachi et al. (U.S. Patent No. 4,265,233), Fisher et al. (U.S. Patent No. 4,556,056), or DE 3007226 and further in view of JP 60117919 and Millan et al. (*Crit. Rev. Clin. Lab. Sci.*, 1995, 32(1):1-39).

(C) Claims 1, 4, 7-9, 27, and 31 stand rejected under 35 U.S.C. §103(a) as being unpatentable over SU 1814764 in view of Sugitachi et al., Fisher et al., or DE 3007226 and further in view of JP 60117919 and Millan et al., and still further in view of WO 92/14480.

(D) Claims 1, 4, 7-9, 27, and 31 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Sugitachi et al., Fischer et al. or DE 3007226 taken with WO 92/14480 and Poelstra et al. (U.S. Patent No. 6,290,952) and further in view of Millan et al.

(7) Arguments

As a preliminary matter, Applicant wishes to bring to the Board's attention a number of issues related to examination of the present application. The following represents a few examples of unnecessary problems that Applicant has encountered to date.

First, many of the Examiner's comments and reasons behind his rejections in Office Actions have been, at best, minimal. For example, in response to Applicants detailed arguments that the cited references do not teach or suggest the claimed invention, the Examiner responded with "fact is, they do." See, for example, the Office Action mailed August 26, 2003 (page 2) and May 18, 2004 (page 4).

In addition, Applicant notes that a Supplemental Response was filed with the U.S. Patent and Trademark Office via facsimile on August 22, 2003. The Supplemental Response of August 22, 2003 was not entered by the Examiner. The Examiner left a phone message on August 23, 2003 for the previous Agent of Record, Dr. Monica McCormick Graham, indicating that he had sent out a Final Office Action and that he was going to throw away the Supplemental Response that had been filed on August 22, 2003. A Final Office Action was mailed on August 25, 2003. Applicant submits that under MPEP §714.05, the Examiner should have entered the amendment and issued a new Office Action. In addition, the Examiner did not provide any reason under MPEP §714.19 for not entering the August 22, 2003 amendment.

Despite the limitations recited in pending claim 1, (e.g., a composition for skin wound healing; an amount of placental alkaline phosphatase effective for stimulating proliferation of fibroblasts), the Examiner has cited and continues to cite references in which alkaline phosphatase (not even placental alkaline phosphatase) is in a gel (e.g., a polyacrylamide gel) for electrophoresis purposes. See, for example, Starkweather, SU 1138410, and SU 1814764. Disclosure of an alkaline phosphatase in an electrophoretic gel is not at all relevant to the claimed invention, yet Applicant is being forced to repeatedly argue over combinations that include this type of disclosure.

Applicant submits that prosecution under this Examiner has prejudiced the Applicant. For example, Applicant has been forced to file seven Responses including responding to two separate Restriction Requirements and the Supplemental Response that was not entered. See the Responses and/or Amendments filed on December 26, 2001, July 23, 2002, December 5, 2002, June 5, 2003, August 22, 2003, November 21, 2003, and February 26, 2004. This amount of prosecution should not be necessary based on the clearly delineated subject matter of the pending claims. Applicant submits that the Examiner has not facilitated prosecution, and has, in the view of Applicant, unnecessarily prolonged and complicated what should have been a relatively straightforward prosecution.

Art Rejections

SU 1138410 discloses recovering placental alkaline phosphatase by extraction, dialysis, and electrophoresis on a polyacrylamide gel. SU 1138410 does not teach or suggest that

placental alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

SU 1814764 discloses a composition for treating burns, ulcers, and infected wounds. The composition disclosed in SU 1814764 is prepared, in part, by passing the composition through a gel of crab extract that also contains DNase, alkaline phosphatase, phosphodiesterase, and protease. SU 1814764 does not teach or suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

The Sugitachi et al. reference discloses that Factor XIII or Factor XIII with thrombin can be attached to structures such as monofilaments, fibrous assemblies, films, or sponges (e.g., gelatin sponges) and applied to a wound site. Factor XIII acts as a fibrin stabilizer and promotes healing of the wound. See, column 1, lines 35-38 and 49-63; and column 3, lines 18-30 of the Sugitachi et al. reference. The Sugatachi et al. reference does not teach or suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

The Fischer et al. reference discloses a bandage material that contains substances important for the treatment and healing of wounds, such as buffer substances, antiseptics, antibiotics, medicinal substances, nutrients, hormones, and local anesthetics. See, column 3, lines 6-18. The bandage material contains a hydrophilic transparent organic gel, which can be a mixture of a hydrophilic polymer and at least one gellable substance of high molecular weight (e.g., agarose or gelatin). See, column 3, lines 28-32 and lines 64-68; and column 4, lines 29-36 of the Fischer et al. reference. The Fischer et al. reference does not teach or suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

The DE 3007226 reference discloses that chlorhexidine and allantoin can be incorporated into gelatin capsules and can exert a synergistic effect on wound healing. DE 3007226 does not teach or suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

JP 60117919 discloses methods of preparing a placenta extract that contains a high concentration of superoxide dismutase. JP 60117919 does not teach or suggest that placental

alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

The Millan et al. reference is a review article on the biology of alkaline phosphatases. The Examiner specifically referred to pages 2 and 3 in the telephone conference of February 12, 2004 to support his obviousness rejection. Pages 2 and 3 of the Millan et al. reference discuss the gene structure of different types of alkaline phosphatase including placental alkaline phosphatase. The Millan et al. reference teaches that placental alkaline phosphatase plays a role in feto-maternal metabolism and placental differentiation (see, for example, pages 17 and 19-21). The Millan et al. reference does not teach or suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

WO 92/14480 discloses a method for promoting accelerated wound healing by administering recombinant G-CSF or recombinant GM-CSF to a wound area. See, page 20, lines 3-7. WO 92/14480 discloses that recombinant G-CSF or recombinant GM-CSF can be combined with another protein such as EGF, FGF, IGF-I, IGF-II, insulin, an interferon, an interleukin, KGF, M-GSF, PD-ECGF, PDGF, SCF, TGF-α, or TGG-β. See, page 20, lines 21-31. It is indicated that each of these proteins may accelerate wound healing. See, page 13, line 1 through page 14, line 12. WO 92/14480 does not teach or suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts and can therefore be used in a topical formulation for skin wound healing.

The Poelstra et al. reference teaches that alkaline phosphatase has endotoxin-detoxifying activity and therefore, can be used systemically to treat or prevent the complications due to infections with Gram-negative bacteria (*e.g.*, sepsis). The compositions disclosed in the Poelstra et al. reference also can be used for promoting bone formation because certain alkaline phosphatases can cause mineralization of the bone matrix and supersaturation of the environment with phosphate. See, for example, column 5, lines 25-35, column 6, lines 15-30, and column 7, lines 8-50. The Poelstra et al. reference teaches systemic administration of alkaline phosphatase and that placental alkaline phosphatase is particularly sutiable for systemic administration. See, for example, column 7, lines 45-47; column 11, lines 3-9 and 22-23; and column 13, line 63 – column 14, line 3. In the telephone conference of February 12, 2004, the Examiner specifically

pointed to column 4, line 53, of the Poelstra et al. reference to support his obviousness rejection. The paragraph at column 4 containing line 53 discloses that:

> "[a] derivative of alkaline phosphatase with fibrillar collagen is not suitable for systemic application as fibrillar collagen induces intravascular platelet activation leading to embolisms. Therefore, a complex of fibrillar collagen and alkaline phosphatase could not be used in a method for treating osteoporosis or osteomalacia or any other bone defect which requires systemic application. It can only be used when immobilized in situ at the location of a wound."

In the context of the Poelstra et al. reference, "***in situ*** at the location of a wound" (emphasis added) refers to directly contacting the bone at the site of a wound. The Poelstra et al. reference does not teach or suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts, and does not teach or suggest that placental alkaline phosphatase can be formulated for topical delivery for healing a skin wound.

Sugitachi et al., Fischer et al., and DE 3007226 were characterized as teaching that "gelatin is known to be used to treat wounds in a topical application." Poelstra et al. was deemed to teach that "alkaline phosphatase is known to be used to treat wounds." WO 92/14480 was characterized as teaching "insulin is known to be used in a composition to topically treat wounds." The Examiner asserted that it "would have been obvious for one of ordinary skill in the art to combine the individual ingredients to form one composition since the ingredients are known individually to be used for the same purpose of treating wounds." The Examiner further asserted that in view of Millan et al., the choice of using placental alkaline phosphatase versus other alkaline phosphatases "is simply the choice of the artisan ... to optimize the desired results."

Applicant strongly disagrees with the Examiner's conclusions. Choosing placental alkaline phosphatases from a relatively large group of tissue-specific and non-tissue-specific alkaline phosphatases is not simply optimization of the desired result. The fact that placental alkaline phosphatase can stimulate the proliferation of fibroblasts was not known prior to the instant disclosure. Therefore, selection of placental alkaline phosphatase is not simply a choice by the artisan to optimize the desired result. As demonstrated by She et al. (*FEBS Letters*, 2000, 469:163-167, a copy of which was submitted with the Response filed on June 5, 2003), placental

alkaline phosphatase stimulated DNA synthesis in fibroblasts, while tissue-non-specific alkaline phosphatase and intestinal alkaline phosphatase did not. See, for example, page 165.

The ***only*** references the Examiner has cited that discloses ***using*** placental alkaline phosphatase is the Poelstra et al. reference, which discloses that placental alkaline phosphatases can be used systemically to prevent sepsis caused by a Gram-negative bacterial infection. Of all the references cited, the Millan et al. reference is the only reference other than the Poelstra et al. reference to even disclose ***placental*** alkaline phosphatase. Even in combination, the Poelstra et al. reference and the Millan et al. reference do not suggest that placental alkaline phosphatase can stimulate proliferation of fibroblasts. In fact, the Millan et al. reference teaches that tissue non-specific alkaline phosphatases (TNAPs) are involved in bone mineralization (see page 18), which suggests that the alkaline phosphatase referred to in column 4 of the Poelstra et al. reference for improving bone mineralization is likely a TNAP.

In addition, a preamble must be read in the context of the entire claim (MPEP §2111.02). A preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference between the claimed invention and the prior art. If so, the recitation serves to limit the claim. See, *e.g., In re Otto*, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963) and *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). Therefore, the preamble reciting a "composition for skin woulnd healing" in combination with the limitation that the composition is "formulated for topical delivery" structurally distinguishes the claimed invention from the disclosures of, for example, SU 1138410 and SU 1814764.

Furthermore, the Examiner has combined references that utilize a gel material in a wound healing composition (Sugitachi et al., Fischer et al., DE 3007226, and WO 92/14480) with references that describe placental alkaline phosphatase (Poelstra et al. and Millan et al.). According to *Interconnect Planning Corp. v. Feil* (744 F.2d 1132, 227 USPQ 543 (Fed. Cir. 1985)), "[i]t is [an] error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a 'blueprint.' When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself." As stated previously, none of the cited references, alone or in combination, teach or suggest using ***placental*** alkaline

phosphatase formulated for ***topical*** delivery in an amount effective to ***stimulate proliferation of fibroblasts*** to treat ***skin*** wounds.

In addition to the fact the cited references do not teach or suggest the claimed invention, the ability of ***placental*** alkaline phosphatase to stimulate production of skin ***fibroblasts*** is an unexpected result. "In the present approaches, contrary to earlier work, it has been discovered that PALP...stimulate[s] proliferation of adult fibroblasts, in particular adult skin fibroblasts." See the sentence bridging pages 5 and 6 of the specification.

Request for Rejoinder

Claims 3, 5, 6, 10, 29, and 30 were withdrawn as directed to a non-elected species following the Restriction Requirement of November 5, 2002 and Applicant's election of December 5, 2002. Since claim 1 should be allowable in view of the remarks herein, Applicant respectfully requests that claims 3, 5, 6, 10, 29, and 30 be rejoined and allowed pursuant to MPEP §809.02(c)(B)(1).

Further, Applicant requests that the Board consider rejoining the claims directed to an article of manufacture containing the composition of claim 1 (essentially corresponding to cancelled claims 32-35). According to the TC1600 Restriction Practice Action Plan (a copy of which was enclosed with the November 21, 2003 Response After Final), the U.S. Patent and Trademark Office plans to publish claim sets that will be examined together regardless of whether they can otherwise be restricted under 35 U.S.C. §121 because the search and examination of the claims do not present a serious burden on the Office. Applicant submits that the claims directed toward articles of manufacture containing the composition recited in pending claim 1 are an example of claims that do not present an additional search burden on the Examiner. Applicant submits that these claims should be entitled to rejoinder. If the Board agrees, Applicant will add the article of manufacture claims by amendment.

A check in the amount of $250 for the Appeal Brief and a check in the amount of $795 for the Petition for Extension of Time are enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: June 17, 2005

M. Angela Parsons, Ph.D.
Reg. No. 44,282

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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Appendix of Claims

1. (Previously Presented) A composition for skin wound healing in a patient comprising placental alkaline phosphatase in an amount effective for stimulating proliferation of fibroblasts and a gel-forming material, wherein said composition is formulated for topical delivery.

2. (Cancelled)

3. (Withdrawn) The composition of claim 1 further comprising a growth factor or a growth promoting serum factor.

4. (Previously presented) The composition of claim 1 further comprising a growth factor selected from the group consisting of PDGF, EGF, FGF, TGF-α, IGF-I, insulin and combinations thereof.

5. (Withdrawn) The composition of claim 1 further comprising serum.

6. (Withdrawn) The composition of claim 1 further comprising an growth promoting serum factor.

7. (Original) The composition of claim 1 wherein the gel-forming material is selected from the group consisting of methyl cellulose, agar, agarose, gelatin, calcium algenate and combinations thereof.

8. (Original) The composition of claim 1 wherein the concentration of the placental alkaline phosphatase is between about 0.001 and about 1 mg/1 gram product.

9. (Original) The composition of claim 1 wherein the concentration of the placental alkaline phosphatase is between about 0.01 and about 0.5 mg/1 gram product.

10. (Withdrawn) The composition of claim 1 further comprising an additive selected from the group consisting of a preservative, a buffer, an antibiotic and a moisture controller.

11-28. (Cancelled)

29. (Withdrawn) The composition of claim 1, wherein the composition is a gel, a lotion, a cream, a rinse, a foam, a mousse, or a spray.

30. (Withdrawn) The composition of claim 1, wherein the composition further comprises PDGF.

31. (Previously presented) The composition of claim 30, wherein the composition further comprises insulin.

32–35. (Cancelled)